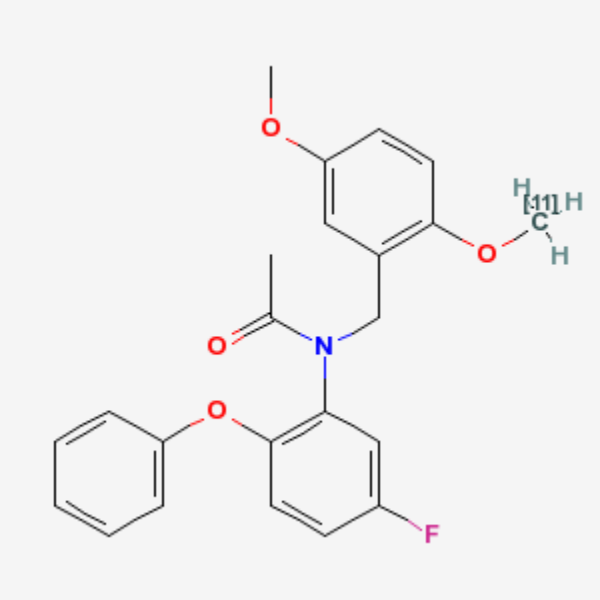
N-(2-[^{11}C],5-Dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide [^{11}C]DAA1106

Created: January 30, 2006
Updated: February 09, 2006

Chemical name: *N*-(2-[^{11}C],5-Dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide
Abbreviated name:
Synonym: [^{11}C]DAA1106
Backbone: Compound
Target: Peripheral-type benzodiazepine receptor
Mechanism: Receptor binding
Method of detection: PET
Source of signal: ^{11}C
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: No
Non-human primate studies: Yes
Human studies: No



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov].

Background

[PubMed]

Benzodiazepines, such as diazepam, are potent psychoactive drugs used for their sedative and anxiolytic properties (1, 2). There are two types of benzodiazepine receptors, which have been identified as the central and peripheral benzodiazepine receptors. The central benzodiazepine receptor (CBR) is found exclusively in the central nervous system on the membranes of neurons and is coupled to the γ-aminobutyric acid receptor/chloride channel (3). In contrast, the peripheral benzodiazepine receptor (PBR) is a mitochondrial protein found in brain and peripheral tissues (adrenal gland, heart, lung, kidney, and testis) (4). The brain has lower levels of PBR than do the peripheral tissues. Both glial cells and macrophages contain high levels of PBR (5-7). Increased

PBR expression after brain injury or neuroinflammation is associated with microglial activation, such as occurs with the neuronal damage accompanying several neurodegenerative diseases, including Alzheimer's disease, Wernicke's encephalopathy, multiple sclerosis, and epilepsy.

PBR has been studied *in vivo* by positron emission tomography (PET) using [^{11}C]PK11195 [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.PK11195-11C], an isoquinoline carboxamide with specific PBR antagonistic activity. [^{11}C]PK11195 is being developed as a PET agent for non-invasive study of microglia and macrophage activation in the brain, lung, and heart. However, accumulation of this tracer in the brain is limited. *N*-(2,5-Dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide (DAA1106) was found to be a selective agonist for studying the PBR in the central nervous system (8, 9). DAA1106 was reported to have a higher affinity for PBR in mitochondrial fractions of rat and monkey brains than did PK11195 (8, 9). Therefore, both tracers are able to cross the normal cell membrane to reach the mitochondrial receptor. [^{11}C]DAA1106 is being developed as a PET agent for the non-invasive study of microglia and macrophage activation in the brain.

Synthesis

[PubMed]

In the report by Zhang et al. (10), [^{11}C]DAA1106 was synthesized by alkylation of the desmethyl precursor (*N*-(5-fluoro-2-phenoxyphenyl) *N*-(2-hydroxy-5-methoxybenzyl)-acetamide) with [^{11}C] methyl iodide in the presence of NaH. Subsequent high-performance liquid chromatography (HPLC) separation gave a radiochemical purity >98% with a total synthesis time of 22 min. The specific activity was 90-156 GBq/μmol (2.5-4.3 Ci/μmol) at end of synthesis. A reproducible radiochemical yield of 72% (decay-corrected) was reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro binding studies of [^{3}H]DAA1106 produced K_d values of 0.12 ± 0.03 and 0.43 ± 0.04 nM for mitochondrial fractions of rat and monkey cerebral cortex, respectively (9). The PBR B_{max} values were 161.03 ± 5.8, and 701 ± 70 fmol/mg protein for mitochondrial fractions of rat and monkey cerebral cortex, respectively. Regional distribution of [^{3}H]DAA1106 in mitochondrial fractions of the rat brain revealed that the olfactory bulb has the highest B_{max} (>400 fmol/mg protein), followed by the cerebellum, cerebral cortex, hypothalamus, striatum, hippocampus, and thalamus. This pattern of DAA1106 binding in the brain was later confirmed by *in vitro* autoradiographic studies using [^{11}C]DAA1106 in rats (11).

Animal Studies

Rodents

[PubMed]

Biodistribution studies in normal mice showed high accumulation of radioactivity in the lung (70.8% of injected dose (ID)/g), followed by the heart (16.5% ID/g), kidney (10.0% ID/g), adrenal gland (6.6% ID/g), and brain (3.5% ID/g) at 15 min after injection of [^{11}C]DAA1106 (10). Radioactivity of the tracer was low in the liver and blood (2% ID/g). The regional distribution in the mouse brain showed rapid accumulation into all brain regions at 1 min post injection. The highest uptake was in the olfactory bulb (4.2% ID/g), followed by the cerebellum (3.5% ID/g), cerebral cortex (2.3% ID/g), striatum (1.8% ID/g), hippocampus (1.7% ID/g), hypothalamus (1.4% ID/g), and thalamus (1.2% ID/g) at 30 min post injection. Coadiministration of unlabeled DAA1106 decreased the accumulation in all brain regions with the most significant reduction in the olfactory bulb and cerebellum. Almost all of the radioactivity in the brain was intact [^{11}C]DAA1106 at 60 min post injection. The fraction of unchanged [^{11}C]DAA1106 in blood samples, as determined by HPLC, was 65% at 5 min, 17% at 30 min, and 6% at 60 min. The major metabolite was found to be the debenzylated compound *N*-(5-fluoro-2-phenoxyphenyl)acetamide, which showed no binding to PBR or CBR (8).

Maeda et al. (11) reported *ex vivo* autoradiographic studies of [^{11}C]DAA1106 brain binding in normal rats and in rats with focal hippocampus lesions induced by kainic acid. [^{11}C]DAA1106 binding was the highest in the olfactory bulb, followed by the cerebellum, pons/medulla, frontal cortex, and hippocampus at 30 min post injection. [^{11}C]DAA1106 binding was increased in the focal hippocampal lesions by 1-fold (P <0.05) over the control hippocampus, indicating an increase in PBR binding sites associated with microglia infiltration.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

Using PET, Maeda et al. (11) obtained serial brain scans in 1 baboon after injections of 90.6 ± 9.3 MBq (2.4 ± 0.3 mCi) of [^{11}C]DAA1106. Accumulation of radioactivity in the brain (occipital cortex, frontal cortex, and cerebellum) was rapid and remained at almost the same level during the 90-min scan. The radioactivity in the occipital cortex was only slightly higher than that in the frontal cortex and cerebellum. Both co-injection and post-treatment injection (30 min after injection of the tracer) of unlabeled DAA1106 (1 mg/kg) or PK11195 (5 mg/kg) enhanced inhibition and displacement of [^{11}C]DAA1106 binding by 80% and 70%, respectively. These results confirmed that these changes represented alterations in specific binding. Specific binding was estimated as 80% of total binding. [^{11}C]DAA1106 binding (0.02% dose/ml) was 3-fold higher than [^{11}C]PK11195 binding (0.005% dose/ml) in the monkey occipital cortex at 30 min post injection partly because of better lipophilicity and higher affinity of [^{11}C]DAA1106. The log P for [^{11}C]PK11195 and [^{11}C]DAA1106 was 2.7 and 3.7, respectively. DAA1106 was reported to have a 2- to 3-fold higher affinity for PBR in mitochondrial fractions of rat and monkey brains than did PK11195 (8, 9).

Human Studies

[PubMed]

No publications are currently available.

References

1. Mohler H, Okada T. Benzodiazepine receptor: demonstration in the central nervous system. Science 198 (4319):849–851; 1977. (PubMed)
2. Hunkeler W, Mohler H, Pieri L, Polc P, Bonetti EP, Cumin R, Schaffner R, Haefely W. Selective antagonists of benzodiazepines. Nature 290(5806):514–516; 1981. (PubMed)
3. Olsen RW, Tobin AJ. Molecular biology of GABAA receptors. FASEB J 4(5):1469–1480; 1990. (PubMed)
4. Anholt RR, Pedersen PL, De Souza EB, Snyder SH. The peripheral-type benzodiazepine receptor. Localization to the mitochondrial outer membrane. J Biol Chem 261(2):576–583; 1986. (PubMed)
5. Jones HA, Valind SO, Clark IC, Bolden GE, Krausz T, Schofield JB, Boobis AR, Haslett C. Kinetics of lung macrophages monitored in vivo following particulate challenge in rabbits. Toxicol Appl Pharmacol 183(1): 46–54; 2002. (PubMed)
6. Kuhlmann AC, Guilarte TR. Cellular and subcellular localization of peripheral benzodiazepine receptors after trimethyltin neurotoxicity. J Neurochem 74(4):1694–1704; 2000. (PubMed)
7. Zavala F, Lenfant M. Benzodiazepines and PK 11195 exert immunomodulating activities by binding on a specific receptor on macrophages. Ann N Y Acad Sci 496:240–249; 1987. (PubMed)
8. Okuyama S, Chaki S, Yoshikawa R, Ogawa S, Suzuki Y, Okubo T, Nakazato A, Nagamine M, Tomisawa K. Neuropharmacological profile of peripheral benzodiazepine receptor agonists, DAA1097 and DAA1106. Life Sci 64(16):1455–1464; 1999. (PubMed)
9. Chaki S, Funakoshi T, Yoshikawa R, Okuyama S, Okubo T, Nakazato A, Nagamine M, Tomisawa K. Binding characteristics of [3H]DAA1106, a novel and selective ligand for peripheral benzodiazepine receptors. Eur J Pharmacol 371(2-3):197–204; 1999. (PubMed)
10. Zhang MR, Kida T, Noguchi J, Furutsuka K, Maeda J, Suhara T, Suzuki K. [(11)C]DAA1106: radiosynthesis and in vivo binding to peripheral benzodiazepine receptors in mouse brain. Nucl Med Biol 30(5):513–519; 2003. (PubMed)
11. Maeda J, Suhara T, Zhang MR, Okauchi T, Yasuno F, Ikoma Y, Inaji M, Nagai Y, Takano A, Obayashi S, et al. Novel peripheral benzodiazepine receptor ligand [11C]DAA1106 for PET: an imaging tool for glial cells in the brain. Synapse 52(4):283–291; 2004. (PubMed)